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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,547	01/23/2002	Arthur L. Castle	GLC0002-US	1223

27189 7590 12/05/2005

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,547	CASTLE ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6-10 and 23-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6-10 and 23-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. The objection to claim 4 in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

Claim Rejections - 35 USC § 112

2. The rejection of claims 6 and 31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

3. The rejection of claims 2-4, 6-10, 23, 24, and 26-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

Claim Rejections - 35 USC § 103

4. The rejection of claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

5. The rejection of claims 2, 11,15, and 33 under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above, and further in view of Holden et al. in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

6. The rejection of claims 2, 10, 26, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9,

11, 13, 14, 24-28, 30, and 32 above, and further in view of Machens et al. in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

7. The rejection of claims 2 and 23 under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above, and further in view of Wikstrom et al. in the Office action mailed 15 April 2005 is withdrawn in view of the amendment filed 18 August 2005.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 2-4, 7-9, 24-28, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al.

The claims are drawn to a method of assessing toxicity of a compound comprising determining the effect of varying both time and dose of a compound on gene expression. In some embodiments the number of genes is greater than 10, the gene expression data is time stable,

contrast analysis, cluster analysis, and principal component analysis is employed, treated liver, kidney, brain, spleen, pancreas, and lung samples are used, the compound is acetaminophen, and factor analysis is used.

Cunningham et al. shows in columns 1-2 a method of comparing the effect of a known toxic compound and a putative toxic compound on gene expression of a treated cell. Microarray polynucleotide hybridization assays are used to assess gene expression. Preferred tissues are listed as liver, kidney, brain, spleen, pancreas, and lung. A preferred toxic compound is acetaminophen. Cunningham et al. shows SEQ ID NOS: 1-61 on column 4 as targets to be assayed for toxic regulation. Cunningham et al. shows clustering of target genes in column 4. As contrast analysis is defined in the specification on page 8 as analysis of genes that are grouped by their response pattern to the toxic compound, Cunningham et al. shows cluster analysis in Tables 1-3 in columns 14-15. Cunningham et al. shows in column 12 that rats were treated for different times with acetaminophen before sacrifice and mRNA isolation. Time variation is a factor analyzed by Cunningham. Time stable is defined in the specification at page 29, lines 17-20, as changes in gene expression in the same direction for two or more time points. Cunningham shows increases in expression in selected genes for two or more time points in Table 1, column 14. Cunningham et al. does not show use of principal component analysis or variation of dose and time.

Hilsenbeck et al. show in the abstract and throughout the use of principal component analysis to determine those genes that varied the most between two experiments. Hilsenbeck et al. treated mice with breast cancer cells, and then treated the mice with tamoxifen. The mice were sacrificed at various times and mRNA was isolated and analyzed by use of a polynucleotide

microarray to assess changes in gene expression during the experiment (see pages 453-454). Hilsenbeck et al. used principal component analysis to determine which genes were the most varied when comparing different mRNA sample sets. Hilsenbeck et al. concludes on page 458 that "principal component analysis of log-transformed data provides a practical approach to data reduction, visualization, and identification of "significant" outlier genes."

Johnston et al. shows in the abstract and especially in figure 4 results of treatment of mice to ozone. A variety of genes were monitored for alterations in gene expression due to the ozone treatment, including eotazin, MIP-1alpha, and MIP-2. The dosage of ozone was varied and time points at each level of ozone were taken. Figure 4 shows that in many instances expression of genes were both dose and time dependent. Johnston et al. concludes on page 95 that early responses to ozone exposure may be predictive of ozone toxicity due to the time and dosage dependence.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. by use of principal component analysis to analyze the gene expression data because Hilsenbeck et al. shows that principal component analysis can be used to analyze gene expression data of toxicity experiments to determine those gene sets that are most varied by the treatment. It would have been further obvious to vary dose and time of treatment because Johnston et al. shows that when toxicity is determined to be time and dose dependent, initial responses may be predictive of later toxicity.

11. Claims 2 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Holden et al.

The claims are drawn to analysis of the effect of carbon tetrachloride on gene expression.

Holden et al. shows treatment of a hepatoma cell line with carbon tetrachloride, followed by isolation of mRNA and polynucleotide microarray analysis of the effect of carbon tetrachloride on gene expression in the treated cells. Forty genes were found to be affected. Holden et al states that their method will allow for study of mechanisms of carbon tetrachloride toxicity.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of carbon tetrachloride as the assayed compound because Holden et al. shows that carbon tetrachloride is a toxic compound that affects gene expression.

12. Claims 2, 10, 26, 28, 29, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Machens et al.

The claims are drawn to analysis toxic compounds on gene expression that uses logistic regression.

Machens et al. shows that use of logistic regression helps in detection of correlation between a patient's HLA genotype and thymic pathology in myasthenia gravis patients. Details of the statistical analysis are given on page 297.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as

applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of the logistic regression method of Machens et al. because Machens et al. shows that their method can be used to correlate genetic data and disease state and for the purposes of the statistical analysis the data of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above is equally applicable to analysis by the method of Machens et al.

13. Claims 2, 23, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Wikstrom et al.

The claims are drawn to analysis toxic compounds on gene expression that uses least squares analysis.

Wikstrom et al. shows that use of least squares analysis helps in detection of correlation of prognostic factors and ultimate development of prostate cancer. The use of least squares analysis is detailed on page 253.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of the least squares analysis method of Wikstrom et al. because Wikstrom et al. shows that their method can be used to correlate prognostic factors and disease state and for the purposes of the statistical analysis the data of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above is equally applicable to analysis by the method of Wikstrom et al.

14. Claims 2, 6, 26, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above, and further in view of Strehlow in view of Lockhart et al.

The claims are drawn to analysis of hybridization signals in which background correction is performed by averaging the background of a region of an array and further by use of mismatch controls.

Strehlow shows software for analysis of microarray data. Strehlow shows background correction that uses either a global average or a local average on page 120.

Lockhart et al. shows use of mismatch hybridization controls to correct for nonspecific hybridization on page 1676.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. as applied to claims 2-4, 7-9, 24-28, 30, and 32 above by use of the local average method of background correction of Strehlow because Strehlow shows that background correction is useful to determine total differences between hybridization samples in an array. It would have been further obvious to use mismatch controls to correct for nonspecific hybridization because Lockhart et al. shows such mismatch controls for each RNA analyzed in their method to correct for nonspecific signal intensity.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD. can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.S. Brusca 27 November 2005

John S. Brusca
Primary Examiner
Art Unit 1631

jsb